Clinical Reports

Failure of neuromuscular blockade reversal after rocuronium in a patient who received oral neomycin

Daniel L. Hasfurther MD, Peter L. Bailey MD

Purpose: *Because the aminoglycoside antibiotics and nondepolarizing muscle relaxants have interactions that vary, it is necessary to update the potential for such interactions when new drugs are introduced clinically. Rocuronium is a newly released steroidal nondepolarizing muscle relaxant with an intermediate duration of action. The following report is the first description of prolonged neuromuscular blockage after rocuronium in a patient who had received oral neomycin in anticipation of open bowel resection.*

Clinical features: *A 71-yr-old woman with a two week history of bleeding pr was scheduled for exploratory laparotomy and right hemicolectomy. She received two standard bowel preparations consisting of oral erythromycin and neomycin over a two day period. Rocuronium was used to facilitate tracheal intubation and maintain muscle relaxation during a two hour operation. Despite clinical appearance of reversal of neuromuscular blockade after neostigmine and glycopyrolate, the patient complained of dyspnoea and weakness upon tracheal extubation and required reintubation twice. The reason for prolonged muscle relaxation was thought to be secondary to a rocuronium and neomycin interaction.*

Conclusion: *Rocuronium, a new nondepolarizing muscle relaxant, has potential interactions with other drugs including the aminoglycoside antibiotics. This clinical report describes the failure of neuromuscular blockade reversal in a patient who received oral neomycin in anticipation of open bowel resection.*

Objectif: *A cause de l'interaction variable des antibiotiques aminosides avec les curares non dépolarisants, il est nécessaire de rechercher ce type d'interactions quand de nouveaux produits deviennent accessibles en clinique. Le rocuronium récemment mis sur le marché est un curarisant non dépolarisant stéroïdien à durée d'action intermédiaire. L'observation qui suit constitue le premier compte rendu d'une curarisation prolongée après l'administration de rocuronium chez une patiente qui avait reçu de la néomycine prophylactique en vue d'une chirurgie coliquen.*

Caractéristiques cliniques: *Une femme de 71 ans possédants des antécédents d'hémorragie rectale était programmée pour une laparotomie exploratrice et une hémicolectomie droite. Elle avait été préparée avec deux prophylaxies intestinales standards d'érythromycine et de néomycine sur une période de deux jours. Du rocuronium avait été administré pour faciliter l'intubation et maintenir la relaxation musculaire pendant l'intervention de deux heure. Malgré l'apparence clinique d'une décurarisation réalisée avec de la néostigmine et du glycopyrrolate, la patiente s'est plainte de faiblesse et de dyspnée et a dû être réintubée à deux reprises. La raison de cette curarisation prolongée est attribuée à l'interaction du rocuronium avec la néomycine.*

Conclusion: *Le rocuronium, un nouveau curare non dépolarisant, possède des interactions potentielles avec d'autres produits dont les antiobiotiques aminosides. Ce compte rendu décrit la décurarisation imcomplète d'une patiente traitée préventivement à la néomycine orale en vue d'une résection intestinale.*

Key words

NEUROMUSCULAR BLOCKING DRUGS: rocuronium, reversal;
DRUG INTERACTIONS: neomycin-rocuronium;
VENTILATORY FAILURE: postoperative.

From The University of Utah, Department of Anesthesiology, 50 North Medical Drive, Salt Lake City, Utah 84132.
Address correspondence to: Dr. Peter L Bailey, The University of Utah, Department of Anesthesiology, 50 North Medical Drive, Salt Lake City, Utah 84132, USA.
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Case study

A 71-yr-old woman presented with a two week history

of bleeding *pr*. Colonoscopic examination revealed a mass between the hepatic flexure and caecum. The patient was scheduled for exploratory laparotomy and right haemicolectomy. Her past medical history included breast cancer, peripheral vascular disease, hypothyroidism, and mild asthma which had been quiescent for years. She had previously undergone a left modified radical mastectomy, aortobifemoral bypass, and a total abdominal hysterectomy with general anaesthesia without complications. Upon admission, medications included tamoxifen, 10 mg *po* BID, and synthroid preparation, 100 μg *po* q day. The patient stated that she had previous allergic reactions to penicillin and macrodantin.

Physical examination revealed a height of 160 cm, and a weight of 55 kg. She had 2+ bilateral carotid bruits, a palpable abdominal mass, and 1+ oedema of her left lower extremity. No symptoms or signs of hypo- or hyperthyroidism were detected. Electrocardiogram revealed normal sinus rhythm at 89 bpm and was otherwise normal. Duplex Doppler examination demonstrated bilateral 30% common carotid artery stenosis. Preoperative electrolyte, magnesium and phosphorus concentrations were normal, and her haematocrit was 29.6%.

The patient received a standard bowel preparation consisting of oral erythromycin and neomycin, one gram each, at 22:00, 23:00 hr the night before, and at 06:00 hr the morning of surgery. After further questioning on the day of surgery, it was noted that she had discontinued her oral synthroid replacement one week before admission. While the patient did not appear clinically hypothyroid, surgery was postponed one day to obtain thyroid function tests (TFTs). These demonstrated a mildly elevated TSH of 10.52 $mU \cdot L^{-1}$ (normal 0.4–5.0), a T_4 of 8.3 $\mu g \cdot dl^{-1}$ (4.5–10.9), and a T_3 uptake of 20% (26–40). In light of the patient's clinical euthyroid state, nearly normal TFT's, and continued blood loss, it was felt best to proceed with surgery and she received a second similar bowel preparation. Preoperative laboratory data on the day of surgery revealed a sodium concentration of 140 $mmol \cdot dl^{-1}$, potassium of 3.9 $mmol \cdot dl^{-1}$, chloride of 116 $mmol \cdot dl^{-1}$, bicarbonate of 20 $mmol \cdot dl^{-1}$, BUN of 5 $mg \cdot dl^{-1}$, creatinine of 1.0 $mg \cdot dl^{-1}$, magnesium of 1.6 $mg \cdot dl^{-1}$, phosphorus of 3.7 $mg \cdot dl^{-1}$, haematocrit of 27.1%, and a platelet count of 294,000 $\cdot \mu l^{-1}$.

In the operating room, a pulse oximeter probe, ECG electrode pads, and an automatic blood pressure cuff were placed. A radial artery catheter was also inserted to monitor blood pressure and permit blood sampling. A foley catheter was placed to monitor urine output. Anaesthesia was induced with sufentanil (50 μg) and etomidate (12 mg) *iv*; rocuronium 40 mg was administered to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane and sufentanil. The lungs were mechanically ventilated with a 2:1 mixture of air and oxygen in addition to ET isoflurane of 0.5 to 1.5%. End-tidal PCO_2 was maintained at 33–38 mmHg.

Neuromuscular blockade was monitored via train-of-four (TOF) count at 2 Hz. The facial nerve was stimulated using 50 mA current and observing the response of the orbicularis oculi muscle. Forty-five minutes after the original dose of rocuronium, three of four (3/4) twitches were noted on facial nerve TOF stimulation and rocuronium (10 mg) was administered. Thirty minutes later, 2/4 twitches were noted and another 10 mg were given, for a total of 60 mg over two hours. At the end of the surgery and 45 min after the last dose of muscle relaxant, the patient had three of four twitches after TOF stimulation and was initiating spontaneous breaths as noted on capnography. Neostigmine 3.5 mg and glycopyrolate 0.4 mg *iv* were administered. Five minutes later, TOF stimulation produced 4/4 twitches and a sustained tetanus could also be elicited. Approximately 10 min after neuromuscular blockade reversal, the patient's mouth was suctioned, she was breathing spontaneously, responded to commands, had a strong grip and the trachea was extubated.

Immediately after extubation, the patient complained of dyspnoea and ventilation was manually assisted by bag and mask. The patient continued to have strong hand grip strength yet was unable to maintain a five second head lift. Additional neostigmine 2 mg and glycopyrolate 0.2 mg *iv* were given. The patient's weakness and dyspnoea persisted. Edrophonium 50 mg and atropine 0.5 mg *iv* were administered without improvement. The possibility of a neomycin induced prolongation of muscle relaxation was considered and calcium chloride 500 mg *iv* was given. The patient's symptoms did not respond to calcium. Arterial blood gas analysis at that time showed pH 7.21, $PaCO_2$ 57 mmHg, and PaO_2 275 mmHg.

Because her dyspnoea was unabated, she was given thiopentone, 125 mg *iv*, and the trachea was reintubated without additional muscle relaxant. Spontaneous ventilation was adequate and the patient was administered supplemental oxygen and taken to the recovery room. Repeat arterial blood gas analysis revealed a pH of 7.33, $PaCO_2$ of 41 mmHg, and a PaO_2 of 380 mmHg. One hour after edrophonium, the patient demonstrated some persistent weakness on head lift. Additional neostigmine 4 mg and glycopyrolate 0.4 mg were administered. Fifteen minutes later, the patient demonstrated a well sustained head lift, tidal volume of 700 ml, and she wanted the tracheal tube removed. Extubation was uneventful, and the patient demonstrated adequate venti-

lation and airway patency. Oxyhaemoglobin saturation was 100% while breathing 3 L O_2 via nasal cannula.

As the patient was about to be discharged from the recovery room, 45 min after receiving the last dose of neostigmine, she again developed shortness of breath and was unable to sustain a head lift. Further doses of neostigmine (3.5 mg) and glycopyrolate (0.6 mg) *iv* were given. However, no improvement in head lift or symptoms occurred. The trachea was again reintubated and she was taken to the ICU where the trachea remained intubated and the lungs were mechanically ventilated overnight. The patient was weaned from the ventilator and the trachea was extubated the following morning without incident and the remainder of her post-operative course was uneventful.

Discussion

Rocuronium is a newly released steroidal nondepolarizing muscle relaxant with an intermediate duration of action. It is less potent but faster acting than vecuronium and has an ED_{95} of approximately 0.4 $mg \cdot kg^{-1}$.[1] Neomycin is an aminoglycoside antibiotic given orally to patients for bowel preparation in anticipation of open bowel surgery. The aminoglycosides are known to extend the neuromuscular blocking effects of muscle relaxants.[2] However, the interaction between aminoglycosides and nondepolarizing muscle relaxants is inconsistant. For instance, Dupuis *et al.* found that gentamycin and tobramycin prolonged the neuromuscular actions of vecuronium but not that of atracurium.[3]

The aminoglycoside antibiotics, and neomycin in particular, have been well studied regarding their ability to produce neuromuscular blockade and prolong the actions of non-depolarizing neuromuscular blocking agents. Studies suggest that neomycin produces neuromuscular blockade by blocking the release of acetylcholine (Ach) at nerve terminals.[4–8] The early work by Elmqvist and Josefsson[4] illustrated that the neuromuscular block produced by neomycin was due to a reduction in the amplitude of the end-plate potential. Neomycin effects at least two sites at the neuromuscular junction. It reduces the amount of transmitter released from the pre-synaptic membrane in response to an action potential. It is thought that neomycin alters calcium influx into the pre-synaptic nerve terminal and thereby reduces the amount of acetylcholine (Ach) released into the synaptic cleft.[4] Experimentally, Elmqvist *et al.* showed an excess of calcium ions antagonized the effect of neomycin.[4] They showed that this was not due to a calcium binding effect, and believed that calcium must interact or compete with neomycin at some step in the pre-junctional process which leads to transmitter release. The administration of calcium to reverse neomycin induced neuromuscular block has been quantified by Singh *et al.*[9] Neomycin also decreases the sensitivity of the post-junctional membrane to the depolarizing actions of Ach, though this is thought to be a less important effect.[5] Our patient received a bowel preparation, which included neomycin, on two consecutive days, and this may explain why she was particularly susceptible to prolonged neuromuscular blockade. Adams *et al.*[10] demonstrated that previous exposure to neomycin potentiated the neuromuscular blocking effect of another subsequent dose of the same antibiotic, even when the residual effects of the previous dose were undetectable by indirect muscle stimulation.

Preoperative laboratory data revealed our patient to be mildly hypothyroid, though she was symptom free and demonstrated no clinical signs of hypothyroidism. While severe hypothyroidism, and especially myxoedema, can contribute to ventilatory difficulties, patients with hypothyroidism do not demonstrate a depressed response to hypercapnia.[11] In addition, because of our patient's clinical euthyroid state, we believe her ventilatory problems were not primarily related to hypothyroidism.

Prior to receiving neostigmine, our patient demonstrated marked recovery from the blockade produced by rocuronium. Following neostigmine and prior to extubation, our patient also had sustained tetanus to facial nerve stimulation. With the patient breathing spontaneously, demonstrating a strong grip strength, and a return of response to command, we had no reason to suspect tracheal extubation would fail because of neuromuscular weakness. Nevertheless, the patient complained of dyspnoea and weakness. Experimental evidence in cats by Lee *et al.*[12] suggest that monitoring the TOF and tetanic response may be inadequate to monitor the degree of neuromuscular blockade in the presence of neomycin. They noted that neomycin produced characteristic train-of-four ratio suppression similar to other neuromuscular blocking agents, yet a tetanic stimulus did not result in characteristic fade. Another unique and possibly important quality of the neuromuscular block produced by neomycin is that it produces post-tetanic exhaustion. This is a phenomenon in which patients who have a prolonged block secondary to neomycin may be able to perform single but not repeated clinical tests of neuromuscular function such as a head lift. This may lead an observer to believe adequate reversal of neuromuscular blockade has been achieved yet when the need for repeated efforts occurs, post-tetanic exhaustion reveals the patient's neuromuscular function to be inadequate. As the patient strains to maintain ventilation and airway patency with repeated tetanic contractions, post-tetanic exhaustion ensues and the patient becomes weak

and unable to support their own airway and/or ventilatory efforts. Repeated clinical tests to assure adequacy of reversal may be helpful in these circumstances.

The role of calcium and neostigmine administration as a potential candidate to reverse the block produced by neomycin has been studied.[9,13,14] Current data suggest that calcium is more reliable and predictable than neostigmine for the reversal of the neuromuscular block produced by neomycin. However, concern has been raised regarding the use of calcium as a reversal agent. Miller *et al.*[15] feel there are two reasons to avoid using calcium in an attempt to reverse the prolonged block produced by certain antibiotics. First, the reversal produced by calcium is not sustained and hence weakness could recur. Secondly, calcium may antagonize the antibacterial effect of antibiotics. They recommend a single reversal dose of neostigmine (60 to 80 $\mu g \cdot kg^{-1}$) as larger doses of anticholinesterases will not produce any greater antagonism.[15] If the reversal is inadequate and the patient continues to demonstrate partial neuromuscular blockade, then ventilatory support should be provided until the block terminates spontaneously. We have no explanation why the first dose of neostigmine given in the recovery room resulted in clinical reversal of residual neuromuscular blockade and permitted tracheal extubation and spontaneous ventilation whereas the second dose given in the recovery room did not. The inconsistent effect of neostigmine supports the conservative, supportive approach to patients experiencing similar problems as perhaps the best recommended course of action.

In conclusion, we believe that this is the first description of rocuronium induced neuromuscular blockade being prolonged and complicated by the effects of neomycin. Because the aminoglycosides and nondepolarizing muscle relaxants have interactions that vary, it is necessary to update the potential for such interactions when new muscle relaxants are introduced clinically. Neomycin produces a characteristic neuromuscular block that demonstrates no tetanic fade to single stimulation yet is susceptible to post-tetanic exhaustion. Because of this characteristic, patients may appear to be adequately reversed when, in fact, they are not. Having patients at risk for neomycin-rocuronium interactions perform a series of clinical tests to determine the adequacy of neuromuscular function may be helpful in such circumstances. If a patient continues to demonstrate signs of inadequate reversal after a single full dose of anticholinesterase, it may be best to continue ventilatory support until the block resolves spontaneously.

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